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(54) Title: HSV PRIMASE INHIBITORS

(57) Abstract

The invention provides compounds of formula (1) that are active against the HSV primase enzyme: wherein R_1 is hydroxy or amino; R_2 is hydrogen, halo, (C_{1-4})alkyl or (C_{1-4})alkoxy; R_3 is hydrogen, halo, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino or azido; R_4 has the same significance as R_2; R_5 is hydrogen or (C_{1-4})alkyl; and R is (C_{1-7})alkyl, (C_{3-6})cycloalkyl, {phenyl(C_{1-7})alkyl}, {phenyl(C_{1-7})alkoxy}, {{(monocyclic heterocyclo)–{(C_{1-7})alkoxy}}, $CH(W)C(O)${O–(C_{1-4})alkyl} wherein W is hydrogen or (C_{1-7})alkyl, or (A) wherein Y is hydrogen or (C_{1-7})alkyl, and Z is (C_{1-7})alkyl, (C_{3-6}) cycloalkyl, {(C_{3-6})cycloalkyl}–{(C_{1-7})alkyl}}, phenyl(C_{1-7})alkyl or {{(monocyclic heterocyclo)–{(C_{1-7})alkyl}}, or Y and Z together with the nitrogen atom to which they are attached represent, 1–pyrrolidinyl, 1–piperidinyl, 4–morpholinyl or 1–(4–methylpiperazinyl); with the provisos that (1) when R is $CH(W)C(O)$–{O–(C_{1-4})alkyl} as defined herein, then R_5 is hydrogen; and (2) at least one of R_2, R_3 and R_4 is other than hydrogen.

HSV PRIMASE INHIBITORS

Technical Field of the Invention

5   This invention relates to methods for inhibiting herpes replication and for
      treating herpes infection in a mammal by inhibiting the herpes primase
      enzyme. In a preferred embodiment, this invention relates to compounds
      that inhibit the primase activity of the herpes helicase-primase enzyme. This
      invention also relates to pharmaceutical compositions comprising the
10   compounds, and to methods of using and producing the compounds.

Background of the Invention

      Herpesviruses are the causative agents of a wide range of diseases
15   suffered by humans and animals. For instance, herpes simplex viruses,
      types 1 and 2 (HSV-1 and HSV-2), are responsible for cold sores and
      genital lesions, respectively; varicella zoster virus (VZV) causes chicken pox
      and shingles; and the human cytomegalovirus (HCMV) is a leading cause of
      opportunistic infections in immunosuppressed individuals.
20
      Herpesviruses are complex double-stranded DNA viruses that encode the
      enzymes that directly mediate viral DNA replication. Seven DNA replication-
      associated polypeptides are required for human herpesvirus replication. Six
      of these seven polypeptides show a high degree of homology across all
25   studied human herpesviruses. These six polypeptides, when expressed by
      the virus, include a heterodimeric DNA-dependent DNA polymerase, a
      monomeric single-stranded DNA binding protein, and a heterotrimeric
      helicase-primase complex that exhibits DNA-dependent ATPase activity,
      helicase activity and primase activity. The seventh DNA replication-
30   associated polypeptide does not display sequence or functional
      conservation and is involved in the initiation of lytic viral replication.

      Without the function of each of the seven herpesvirus-specific DNA
      replication proteins, herpesvirus chromosomal replication will not initiate or

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propagate. This has been demonstrated in two ways for DNA replication in HSV-1. First, temperature sensitive HSV-1 strains have been developed and the complementation groups within these strains have been mapped on a one-to-one correspondence to the seven HSV DNA replication genes.

5   Additionally, transient replication assays that utilized recombinant DNA plasmids containing single DNA replication genes have found that the presence of each of the seven genes was required for the efficient replication of a tester plasmid containing an HSV-1 origin of DNA replication.

10 More recently, the DNA replication genes in other herpesviruses (i.e., Epstein-Barr virus, cytomegalovirus and varicella zoster virus) have been sequenced. These gene sequences are largely homologous to the HSV-1 DNA replication genes. Furthermore, transient replication assays containing either an Epstein-Barr virus or cytomegalovirus lytic origin of DNA replication

15 confirmed their identity. In varicella zoster virus (the human herpesvirus most closely related to HSV-1) DNA replication genes were found to be highly homologous to HSV-1 (>50% at the amino acid level) and present at identical relative locations on the two viral chromosomes. Although no follow-up analysis on varicella zoster virus DNA replication genes has been

20 presented to date, it is highly unlikely that differences in the varicella zoster virus and HSV-1 DNA replication programs exist.

From the above, it is clear that human DNA replication proteins are unable to substitute for the HSV-1 encoded enzymes. Otherwise, temperature-

25 sensitive viral polypeptides would have been complemented by human counterparts and the defective viruses would have continued to grow and replicate, even at elevated temperatures. Similarly, in transient replication assays, if human proteins were capable of complementing any of the seven herpesvirus-encoded polypeptides, an absolute dependence on the

30 presence of each of these herpesvirus DNA replication-specific genes would not have been observed. Therefore, inhibiting the activity of these virally-encoded proteins represents an effective way of preventing herpesviral replication.

The herpes primase enzyme plays a critical role in the herpesvirus DNA replication program. The observation that the gene encoding the herpes primase is not only essential for replication, but is also highly conserved across the range of known herpesviruses, underscores the importance of

5   this enzyme in mediating viral chromosomal replication.

In the helicase-primase complex, two of the three polypeptides (e.g., the expression products of the UL5 and UL52 genes of HSV-1) promote catalysis of duplex DNA unwinding (helicase) and RNA primer biosynthesis

10   (primase). The third polypeptide, encoded by the UL8 gene, appears to modulate primase activity. The assembled helicase-primase enzyme complex functions both in the initiation and propagation stages of herpesvirus DNA replication. It is responsible for the synthesis of RNA primers necessary for the initiation of all new DNA synthesis by the

15   herpesvirus DNA polymerase. Additionally, for DNA replication to proceed, duplex viral chromosomal DNA must first be unwound to the single-stranded replicative intermediate because the herpesvirus DNA polymerase is inactive on fully duplex DNA. The helicase-primase is also responsible for this important DNA unwinding event.

20

Known anti-herpes therapies have not focused on inhibiting the primase activity of the herpes helicase-primase. The most widely used anti-herpes agents to date are purine and pyrimidine nucleoside analogs, such as acyclovir and ganciclovir. These nucleoside analogues inhibit replication of

25   viral DNA by their incorporation into a growing DNA strand. The nucleoside analogue-based inhibitors of HSV-1 growth have found only limited success and are not generally useful in treating recurring infections in the majority of patients. In addition, the infection of humans by other herpesviruses, such as varicella zoster virus or cytomegalovirus, show little or no responsiveness

30   to nucleoside-based therapies.

The lack of broad spectrum anti-herpesvirus activity by the nucleoside-based therapies is not surprising because these compounds act by indirect biological mechanisms. Nucleoside analogues must first be activated to the

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nucleoside monophosphate by a virally-encoded thymidine kinase enzyme.
It should be pointed out that only HSV and varicella zoster virus encode
thymidine kinase enzymes. This may, in part, explain the inability to adapt
nucleoside-based therapies to the treatment of other human herpesviruses.

5   After initial phosphorylation, the nucleoside analogue monophosphate must
be further phosphorylated to the triphosphate by human-encoded enzymes
prior to its action. Ultimately, the triphosphorylated nucleoside analogue is
incorporated into a nascent DNA chain during viral genomic replication,
thereby inhibiting the elongation of that DNA chain by the herpes DNA

10   polymerase.

The final incorporation step of the nucleoside-based therapies has been
characterized as "competitive" because the herpes DNA polymerase does
not display a preference for the activated nucleoside drug versus normal

15   deoxynucleoside triphosphates. However, because the action of the DNA
polymerase is not considered rate-limiting for herpesvirus DNA replication,
the utility of nucleoside-derived compounds in treating herpesvirus infections
is necessarily limited. Accordingly, the need for effective, safe therapeutic
agents for treating herpesvirus infections continues to exist.

20
References disclosing N-(carbonylphenyl)benzamide derivatives include the
following:

A.A. Patchett et al., Canadian patent 793,882, September 3, 1968,

25   R.A. Coburn et al., US patent 4,358,443, November 9, 1982,
P.R. Andrews et al., Australian Journal of Chemistry, **1988**, 41, 493,
W.A. Harrison et al., European patent application 497 816, May 17, 1995,
H. Setoi et al., PCT patent application WO 96/41795, published December
27, 1996,

30   M. Teng et al., PCT patent application WO 97/19062, May 29, 1997,
J.-M. Bernardon, PCT patent application WO 98/34909, published August
13, 1998, and
W.A. Harrison et al., US patent 5,693,827, December 2, 1997.

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Summary of the Invention

In a first aspect, the invention provides compounds of the formula 1
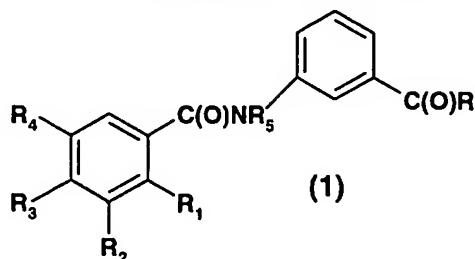
5   wherein

R_1 is hydroxy or amino;

R_2 is hydrogen, halo, (C_{1-4})alkyl or (C_{1-4})alkoxy;

R_3 is hydrogen, halo, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino or azido;

R_4 has the same significance as R_2;

10   R_5 is hydrogen or (C_{1-4})alkyl; and

R is (C_{1-7})alkyl, (C_{3-6})cycloalkyl, {phenyl(C_{1-7})alkyl}, {phenyl(C_{1-7})alkoxy}, {{(monocyclic heterocyclo)-

{(C_{1-7})alkoxy}}, CH(W)C(O){O-(C_{1-4})alkyl} wherein W is hydrogen or (C_{1-7})alkyl, or

15   wherein Y is hydrogen or (C_{1-7})alkyl, and Z is (C_{1-7})alkyl, (C_{3-6})cycloalkyl, {(C_{3-6})cycloalkyl}-

{(C_{1-7})alkyl}, phenyl(C_{1-7})alkyl or {{(monocyclic heterocyclo)-{(C_{1-7})alkyl}}, or

Y and Z together with the nitrogen atom to which they are attached

represent, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or 1-(4-

20   methylpiperazinyl);

with the provisos that (1) when R is CH(W)C(O)-

{O-(C_{1-4})alkyl} as defined herein, then R_5 is hydrogen; and (2) at least one of

R_2, R_3 and R_4 is other than hydrogen.

25   A preferred group of compounds is represented by formula 1 wherein

R_1 is hydroxy or amino,

R_2 is hydrogen or halo,

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R_3 is hydrogen, halo, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino or azido,

R_4 is hydrogen or halo,

R_5 is hydrogen or (C_{1-4})alkyl, and

R is (C_{1-7})alkyl, (C_{3-6})cycloalkyl,

phenyl{(C_{1-7})alkyl}, {phenyl(C_{1-7})alkoxy}, {(monocylic heterocyclo){(C_{1-7})alkoxy}}, CH(W)C(O)-{O-(C_{1-4})alkyl} wherein W is hydrogen or (C_{1-7})alkyl, or

$$N \overset{Y}{\underset{Z}{<}}$$

wherein Y is hydrogen and Z is (C_{1-7})alkyl,

(C_{3-6})cycloalkyl, {(C_{3-6})cycloalkyl}-{(C_{1-7})alkyl}, phenyl{(C_{1-7})alkyl}, or {(monocyclic heterocyclo)-{(C_{1-7})alkyl}, or Y and Z together with the nitrogen atom to which they are attached represent 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or 1-(4-methylpiperazinyl).

A more preferred group of compounds is represented by formula 1 wherein

R_1 is hydroxy or amino,

R_2 is hydrogen or chloro,

R_3 is hydrogen, chloro, methyl, methoxy, amino or azido,

R_4 is hydrogen, chloro or iodo,

R_5 is hydrogen or methyl, and

R is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, cyclohexyl, phenylmethyl, 2-phenylethyl, phenylmethoxy, 2-phenylethoxy, 2-, 3- or 4-pyridinylmethoxy, 2-(2-,3- or 4-pyridinyl)ethoxy, $CH_2C(O)\{O-\{(C_{1-4})$alkyl}}, CH{(C_{1-7})alkyl}C(O){OC_{1-4})alkyl}, (C_{1-7})alkylamino, cyclopentylamino, cyclohexylamino, (cyclohexylmethyl)amino, (2-cyclohexylethyl)amino, (phenylmethyl)amino, (2-phenylethyl)amino, 2-(3- or (4-pyridylmethyl)amino or 2-(2-, (3- or (4-pyridylethyl)amino.

A most preferred group of compounds is represented by formula 1 wherein

R_1 is hydroxy,

R_2 is hydrogen,

R_3 is methyl, methoxy, amino or azido,

R_4 is hydrogen, chloro or iodo,

R_5 is hydrogen, and

R is pentyl, hexyl, cyclohexyl, phenylmethyl, 2-phenylethyl, phenylmethoxy, 2-, 3- or 4-pyridinylmethoxy, $CH_2C(O)OCH_2CH_3$, $CH(CH_2CH_2CH_2CH_3)C(O)OCH_2CH_3$, ethylamino, propylamino, butylamino,

5   cyclohexylamino, (cyclohexylmethyl)amino, (2-cyclohexylethyl)amino, (phenylmethyl)amino, (2-phenylethyl)amino, or (2-, (3- or (4-pyridyl-methyl)amino, or 2-(2-, (3-, or (4-pyridinylethyl)amino.

A further objective of this invention is to provide compounds useful in the

10   methods of this invention and for pharmaceutical compositions comprising those compounds.

Another objective of this invention is to provide processes for preparing the compounds of this invention.

15

Still a further objective of this invention is to provide pharmaceutical compositions containing the compounds of this invention and methods for treating herpes infection in a mammal using those pharmaceutical compositions.

20

Detailed Description of the Invention

The invention described herein overcomes the limitations associated with known anti-herpes agents, by providing non-nucleoside-based inhibitors of

25   herpes replication, i.e. N-(3-carbonylphenyl)benzamide derivatives. Without being bound to theory, it is believed that the compounds of the invention act directly in interfering with the likely rate-limiting process in herpesvirus DNA replication: the action of the herpes primase enzyme. Furthermore, since the herpesvirus primase enzyme is conserved across the human

30   herpesviruses, compounds of this invention are effective against other herpesviruses, including HSV and varicella zoster virus, and also against nucleoside-nonresponsive and nucleoside-resistant herpes infections.

As used herein, the following definitions apply unless otherwise noted:

8

The term "herpes" as used herein refers to a herpes virus while encodes the herpes primase of HSV-1, and to those herpesviruses that encode a herpes primase homologous to the herpes primase of HSV-1. The herpes family of viruses includes, but is not limited to, HSV-1, HSV-2, varicella zoster virus and Epstein-Barr virus.

The term "halo" as used herein means a halo radical selected from bromo, chloro, fluoro or iodo.

The term "(C_{1-4})alkyl" as used herein, either alone or in combination with another radical, means alkyl radicals containing from one to four carbon atoms and includes methyl, ethyl, propyl and 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl.

The term "(C_{1-7})alkyl" as used herein means straight and branched chain alkyl radicals containing from one to seven carbon atoms and includes ethyl, butyl, 1-methylpropyl, 1-ethylpropyl, 2,2-dimethylpropyl, 1-ethylbutyl, 2-ethyl-2-methylbutyl, 2-ethylbutyl, 1-propylbutyl, 2-propylbutyl and the like.

The term "(C_{3-6})cycloalkyl" as used herein, either alone or in combination with another radical, means saturated cyclic hydrocarbon radicals containing from three to six carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "(C_{1-4})alkoxy" as used herein means straight chain alkoxy radicals containing one to four carbon atoms and branched chain alkoxy radicals containing three to four carbon atoms and includes methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. The latter radical is known commonly as *tert*-butoxy.

The term "(C_{1-7})alkoxy" as used herein, either alone or in combination with another radical, means straight chain alkoxy radicals containing one to seven carbon atoms and branched chain aloxy radicals containing from

three to seven carbon atoms and includes the alkoxy group noted in the preceding paragraph, as well as pentyloxy, hexyloxy, 1-propylbutoxy and the like.

5   The term "amino" as used herein means an amino radical of formula -NH$_2$. The term "(C$_{1-7}$)alkylamino" as used herein means an alkylamino radicals containing one to seven carbon atoms and includes methylamino, propylamino, (1-methylethyl)amino and (2-methylbutyl)amino.

10   The term "monocyclic heterocyclo" as used herein means a monovalent radical derived by removal of a hydrogen from a five- or six-membered saturated or unsaturated heterocycle; said five-membered heterocycle may contain up to four nitrogen atoms (for example tetrazolyl), or said five- or six-membered heterocycle may contain from one to three heteroatoms selected

15   from nitrogen, oxygen and sulfur. Optionally, the heterocycle may bear one or two substituents; for example, N-oxido, (C$_{1-4}$)alkyl, phenyl(C$_{1-4}$)alkyl, (C$_{1-4}$)alkoxy, halo, amino or (C$_{1-7}$)alkylamino. Examples of suitable heterocycles and optionally substituted heterocycles include pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, 1H-imidazole, 1-methyl-1H-imidazole, pyrazole, furan,

20   thiophene, oxazole, isoxazole, thiazole, 2-methylthiazole, 2-aminothiazole, 2-(methylamino)-thiazole, piperidine, 1-methylpiperidine, 1-methylpiperazine, 1,4-dioxane, morpholine, pyridine and pyridine N-oxide.

The term "pharmaceutically acceptable carrier" or "veterinarily acceptable

25   carrier" as used herein means a non-toxic, generally inert vehicle for the active ingredient which does not adversely affect the ingredient.

The term "effective amount" means an antiviral amount of the antiviral agent, i.e. an amount of the agent sufficient to be effective against the virus

30   in vivo.

10

Processes for preparing the compounds

The compounds of this invention can be prepared by a variety of
conventional processes. Description of some such processes are found in
5   standard textbooks such as "Annual Reports In Organic Synthesis - 1996",
P.M. Weintraub et al., Eds., Academic Press, Inc., San Diego, CA, USA,
1996 (and the preceding annual reports), "Vogel's Textbook of Practical
Organic Chemistry", 5th Ed., B.S. Furniss et al., Eds., Longman Group
Limited, Essex, UK, 1989, and "Comprehensive Organic Synthesis", B.M.
10   Trost and I. Fleming, Eds., Pergamon Press, Oxford, UK, 1991, Volumes 1
to 8.

A process for preparing a compound of formula 1 wherein R is (C_{1-7})alkyl,
(C_{3-6})cycloalkyl, phenyl or phenyl$\{(C_{1-7})$alkyl is represented by Scheme 1
15   wherein R_A is (C_{1-7})alkyl or phenyl$\{(C_{1-7})$alkyl$\}$, R_{1A} is
(C_{1-4})alkoxy or nitro, R_2 and R_4 each is hydrogen, halo, (C_{1-4})alkyl or (C_{1-4})alkoxy, R_{3A} is hydrogen, halo, (C_{1-4})alkyl, (C_{1-4})alkyl, nitro or azido and R_B is
(C_{1-7})alkyl, (C_{3-6})cycloalkyl, phenyl or
phenyl$\{(C_{1-7})$alkyl$)$.

20

Scheme 1
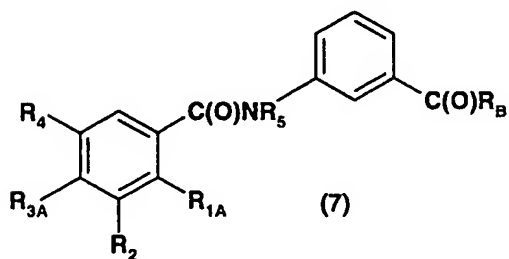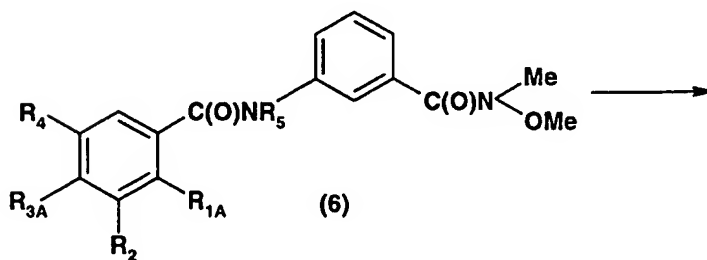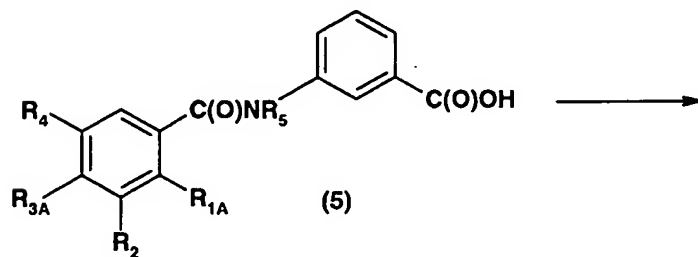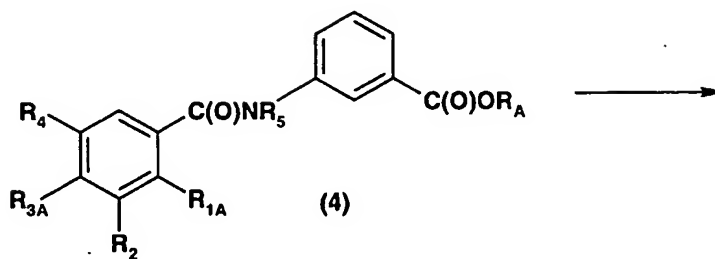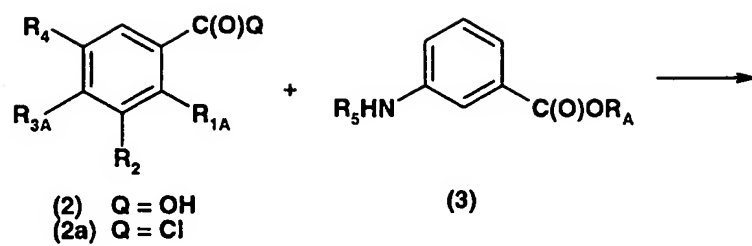
(2)   Q = OH
(2a)   Q = Cl

(3)

(4)

(5)

(6)

(7)

12

Corresponding compound of formula 1 wherein R is (C_{1-7})alkyl, (C_{3-6})cycloalkyl, phenyl or {phenyl(C_{1-7})alkyl}, R_1 is hydroxy or amino, R_3 is hydrogen, halo, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino or azido.

5

With reference to Scheme 1, a substituted benzoic acid of formula 2 is converted to its corresponding acid chloride 2a and the latter is reacted with an aminobenzoate of formula 3, in the presence of an acid scavanger such as triethylamine, to yield a benzoylaminobenzoate of formula 4. The latter

10   compound is subjected to a basic hydrolyzing agent (e.g. aqueous sodium hydroxide) to yield the corresponding benzoic acid derivative of formula 5. Thereafter, the benzoic acid derivative 5 is coupled with N,O-dimethylhydroxylamine in the presence of a coupling agent to obtain the corresponding N-methoxy-N-methylbenzamide of formula 6. In turn, the N-

15   methoxy-N-methylbenzamide is reacted with either an appropriate Grignard reagent of formula R_B-Mg-(halo) or organolithium reagent of formula R_B-Li wherein R_B is (C_{1-7})alkyl, (C_{3-6})cycloalkyl, phenyl or phenyl{(C_{1-7})alkyl}, according to the acylating method of S. Nahm and S.M. Weinreb, Tetrahedron Letters, **1981**, *22*, 3815, to give the corresponding

20   benzoylaminobenzoyl derivative of formula 7.

Subsequent ether cleavage of the alkoxy of R_{1A}, if present, with aluminium chloride in a inert solvent such as methylene dichloride, benzene or carbon tetrachloride; or reduction of the nitro group of R_{1A} and/or R_{3A} if present with

25   an appropriate reducing agent, preferably triethylsilane in the presence of Wilkinson's catalyst, i.e. $RhCl(PPh_3)_3$, described by H.R. Brinkman, Synthetic Communications, **1996**, *26*, 973, in an inert aromic solvent such as benzene or toluene; transforms the benzoylaminobenzoyl derivative of formula 7 into the corresponding desired compound of formula 1 wherein R

30   is

(C_{1-7})alkyl, (C_{3-6})cycloalkyl, phenyl or

phenyl{(C_{1-7})alkyl} and R_1 and R_3 are as defined herein.

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The coupling of the benzoic acid derivative of formula 5 and N,O-
dimethylhydroxylamine is effected by the classical dehydrative coupling of a
free carboxyl of one reactant with the free amino group of the other reactant
5   in the presence of coupling agent to form a linking amide bond. Description
of such coupling agents are found in general textbooks on peptide
chemistry; for example, M. Bodanszky, "Peptide Chemistry", 2nd rev ed,
Springer-Verlag, Berlin, Germany, 1993. Examples of suitable coupling
agents are N,N'-dicyclohexyl-carbodiimide, 1-hydroxybenzotriazole in the
10   presence of N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-{(3-
dimethylamino)propyl}carbodiimide. A very practical and useful coupling
agent is the commercially available (benzotriazol-1-yloxy)tri-
(dimethylamino)phosphonium hexafluorophosphate, either by itself or in the
presence of 1-hydroxybenzotriazole. Still another very practical and useful
15   coupling agent is commercially available 2-(1H-benzotriazol-1-yl)-N,N,N',N'-
tetramethyl-uronium tetrafluoroborate.

The coupling reaction is conducted in an inert solvent, e.g. dichloromethane,
dimethylformamide, tetrahydrofuran or acetonitrile. A base, such as a
20   tertiary amine, e.g. diisopropylethylamine or N-methylmorpholine, may be
added. The reaction temperature usually ranges between 0° and 50° and
the reaction time usually ranges between 15 min and 24 h.

Alternatively, the N-methoxy-N-methyl benzamide of formula 6 wherein R_5 is
25   hydrogen can be readily N-alkylated (at the secondary amide) by
conventional methods to give the corresponding N-methoxy-N-methylamide
of formula 6 wherein R_5 is (C_{1-7})alkyl.

The latter N-alkylated amido derivative can then be transformed to a
30   corresponding compound of formula 1 as described hereinbefore via the
step sequence represented by formula 6→7→1.

A process for preparing a compound of formula 1 wherein R is hydroxy and
R_1 is hydroxy, involves cleavage of the ether with aluminum chloride of the

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appropriate benzoic acid of formula 5 wherein R_{1A} is (C_{1-4})alkoxy, in the manner described previously, to obtain the corresponding compound of formula 1 wherein R is hydroxy and R_1 is hydroxy.

5   A compound of formula 1 wherein R is (C_{1-7})alkoxy or phenyl{(C_{1-7})alkoxy} and R_1 and/or R_3 is amino can be prepared by reducing the corresponding benzoylamino benzoate of formula 4 wherein R_1 and/or R_3 is nitro, according to the nitro group reduction method described previously, to obtain the corresponding compound of formula 1 wherein R is

10   (C_{1-7})alkoxy or phenyl{(C_{1-7})alkoxy} and R_1 and/or R_3 is amino.

A process for preparing a compound of formula 1 wherein R is $CH(W)C(O)\{O-(C_{1-4})alkyl\}$ wherein W is hydrogen or (C_{1-4})alkyl can be represented by Scheme 2 wherein W_A is (C_{1-4})alkyl R_C is (C_{1-4})alkoxy and

15   R_{1A}, R_2, R_{3A} and R_4 are as defined herein.

Scheme 2

Corresponding compound of formula 1
wherein R is $CH_2C(O)\{O-(C_{1-4})alkyl\}$

Corresponding compound of formula 1 wherein
R is $CH\{(C_{1-7})alkyl\}C(O)-\{O-(C_{1-4})alkyl\}$

15
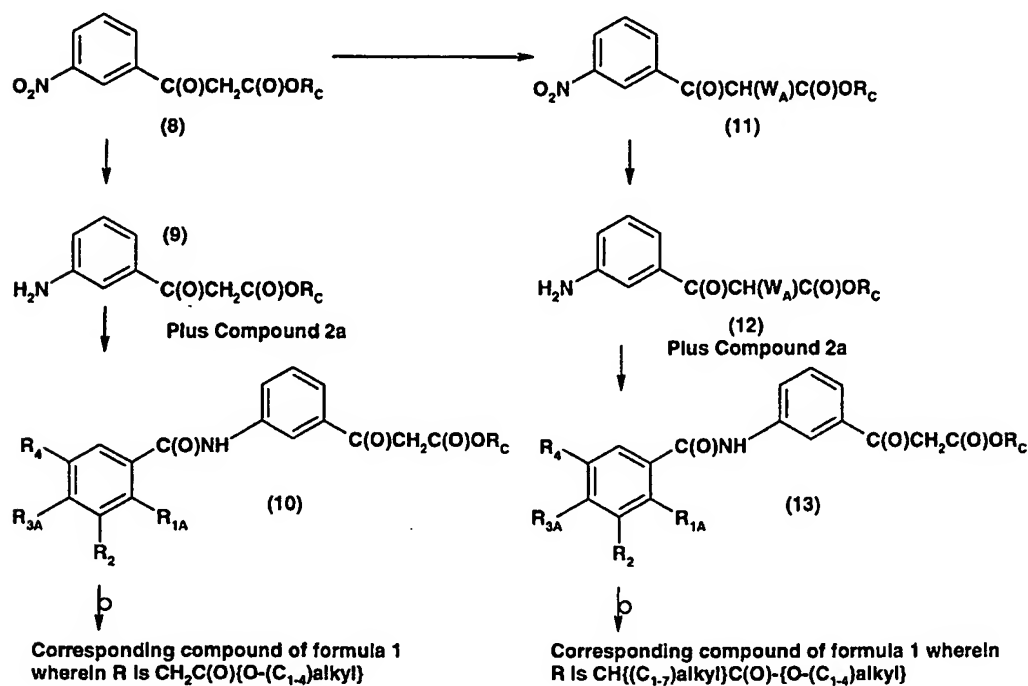
With reference to Scheme 2, the nitro-β-ketoester of formula 8 is subjected to catalytic hydrogenation (e.g. H_2 in the presence of Pd/BaSO$_4$) to afford the amino-β-ketoacid of formula 9 which in turn is reacted with the acid chloride 2a in the presence of an acid scavanger, e.g. triethylamine, to yield
5   the β-ketoester of formula 10.

Thereafter, with reference to the latter β-ketoester, the ether cleavage of the R_{1A} (C$_{1-4}$)alkoxy group, if present, or the reduction of the R_{1A} and/or R_{3A} nitro group, if present, in the manner described above for such cleavages and
10   reductions affords the desired compound of formula 1 wherein R is $CH_2C(O)(O-(C_{1-4})$alkyl) and R_1 is hydroxy or amino respectively.

Likewise, following the route illustrated by the compound sequence of 8 → 11 (via C-alkylation) → 12 → 13 → corresponding compounds of formula 1,
15   a desired compound of formula 1 wherein R is CH{(C$_{1-7}$)alkyl)C(O){O-(C$_{1-4}$)alkyl} and R_1 is hydroxy or amino can be obtained.

A variation of the previous Scheme for obtaining a compound of formula 1 wherein R is
20   CH{(C$_{1-7}$)alkyl}C(O){O-(C$_{1-4}$)alkyl} and R_1 is hydroxy is illustrated in Scheme 3:

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Scheme 3

O_2N —⬡— $C(O)CH_2C(O)OEt$ ⟶

(14)

O_2N —⬡— $C(O)CH(CH_2CH=CHMe)C(O)OEt$ ⟶

(15)

H_2N —⬡— $C(O)CH(CH_2CH_2CH_2Me)C(O)OEt$

(16)

$C(O)Cl$
⬡   (17)
Cl OH

Cl —⬡— $C(O)NH$ —⬡— $C(O)CH(CH_2CH_2CH_2Me)C(O)OEt$
  OH

(18)   a compound of formula 1
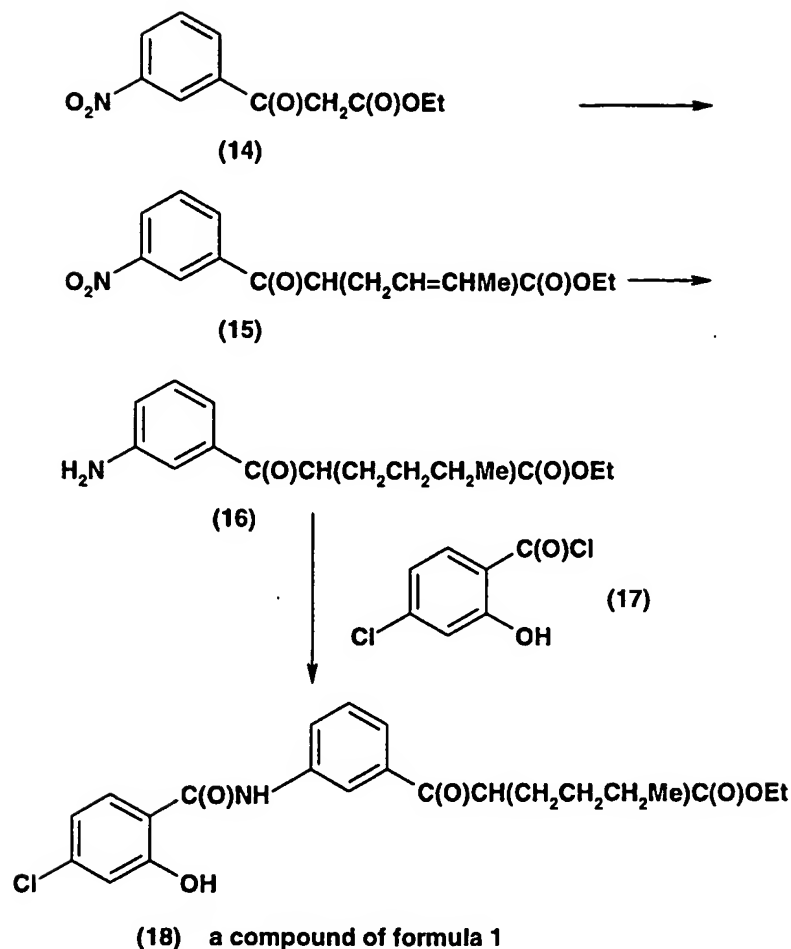
With reference to Scheme 3, the key steps are (a) the alkylation of β-
ketoester 14 with 1-bromo-2-butene in the presence of sodium hydride, (b)
5   the reduction of the nitro group and side chain double bond of the
intermediate 15, and (c) the coupling of intermediate 16 with the salicylic
acid derivative 17 having an unprotected (free) hydroxyl. This variation is
described in detail in the experimental hereinafter. Also, noteworthy at this
point is that treatment of compound 18 with lithium hydroxide, followed by
10   acid hydrolysis, yields the compound of formula 1 in which R is pentyl, R_1 is

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hydroxy, R_2 and R_4 each is hydrogen and R_3 is chloro. See the experimental hereinafter.

A process for preparing a compound of formula 1 wherein R is

$$N\overset{Y}{\underset{Z}{<}}$$

5   wherein Y is hydrogen or (C_{1-7})alkyl and Z is (C_{1-7})alkyl, (C_{1-6})cycloalkyl, {(C_{3-6})cycloalkyl}

{(C_{1-7})alkyl}, phenyl(C_{1-7})alkyl or {(monocyclic heterocyclo)alkyl}, or Y and Z together with the nitrogen atom to which they are attached represent 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or 1-(4-methylpiperazinyl); can be

10   represented by Scheme 4, wherein

$$N\overset{Y}{\underset{Z}{<}}$$

, R_{1A}, R_2, R_{3A} and R_4 are as defined herein.

Scheme 4
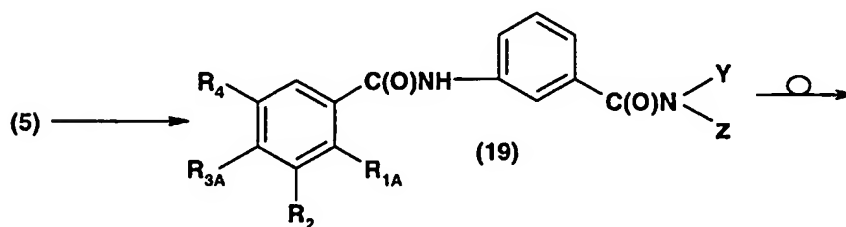
15   Corresponding compound of formula 1 wherein R is $N\overset{Y}{\underset{Z}{<}}$ wherein Y and Z are as defined herein.

According to Scheme 4, the benzoic acid derivative of formula 5 is reacted with the appropriate amine of formula

$$HN\overset{Y}{\underset{Z}{<}}$$

20   wherein Y and Z are as defined herein in the presence of a coupling agent to give the corresponding benzoylaminobenzamide of formula 19 Subsequently, for a compound of formula 19 having a (C_{1-4})alkoxy group at R_{1A}, the compound is subjected to the previously noted ether cleavage

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conditions (i.e. aluminium chloride in an inert solvent at room temperature)
to give the corresponding compound of formula 1 wherein R is
$N\stackrel{Y}{\underset{Z}{<}}$
as defined herein and R_1 is hydroxy; or for a compound of formula 19
having a nitro group at R_{1A}, and/or R_{3A}, the compound is subjected to the

5   previously described nitro reduction method, i.e. with triethylsilane and
$RhCl(PPh_3)_3$, to give the corresponding compound of formula 1 wherein R is
$N\stackrel{Y}{\underset{Z}{<}}$
as defined herein and R_1 is amino and R_3 is as defined herein

The starting materials for the preceding processes are known or can be

10   prepared readily from known compounds. A number of the substituted
benzoic acids of formula 2 and the aminobenzoates of formula 3 (or their
corresponding acids) are available from the Aldrich Chemical CO.,
Milwaukee, WI, USA.

15   The chemical reactions described above are generally disclosed in terms of
their broadest application to the preparation of the compounds of this
invention. Occasionally, the reactions may not be applicable as described to
each compound included within the disclosed scope. The compounds for
which this occurs will be readily recognized by those skilled in the art. In all

20   such cases, the reaction can be successfully performed by modifications
known to those skilled in the art, e.g. by appropriate protection of interfering
groups, by changing to alternative reagents, by modification of reaction
conditions, or by modification illustrated in the examples herein such as
preparing compounds of formula 1 wherein R_3 is amino by using appropriate

25   intermediates wherein R_{3A} is nitro and reducing the nitro group to finally
obtain the corresponding compound of formula 1 wherein R_3 is amino.

If desired, compounds of formula 1 having a basic nitrogen atom can be
obtained in the form of acid addition salts. Such salts can be considered as

30   biological equivalents of the compounds of formula 1. For therapeutic
applications, it is preferred to use pharmacuetically acceptable salts.

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Examples of such salts are those formed with hydrochloric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid or citric acid.

Antiherpes Activity

5

The antiviral activity of the compounds of formula 1 can be demonstrated by biochemical, microbiological and biological procedures showing the inhibitory effect of the compounds on the replication of herpes simplex viruses, types 1 and 2 (HSV-1 and HSV-2), as well as acyclovir-resistant

10   herpes simplex viruses and ganciclovir-resistant cytomegaloviruses.

A biochemical procedure for demonstrating antiherpes activity for compounds of formula 1 is described in the examples hereinafter. This particular assay is based on the evaluation of the ability of the test

15   compound to inhibit HSV-1 primase, an essential enzyme for viral DNA replication.

Methods for demonstrating the inhibitory effect of the compounds of formula 1 on herpes viral replication involving *in vitro* and cell culture techniques are

20   described in the examples.

The therapeutic effect of the compounds of formula 1 can be demonstrated in laboratory animals, for instance, the hairless mouse model for the topical treatment of cutaneous HSV-1 infections, P.H. Lee et al., International

25   Journal of Pharmaceutics, **1993**, *93*, 139; the (HSV-2)-induced genitalis mouse model, R.W. Sidewell et al., Chemotherapy, **1990**, *36*, 58; and BALB/C mouse model infected with murine cytomegalovirus, D.L. Barnard et al., Antiviral Res., **1993**, *22*, 77, and J. Neyts et al., Journal of Medical Virology, **1992**, *37*, 67.

30

When a compound of formula 1, or one of its therapeutically acceptable acid addition salts, is employed as an antiviral agent, it is administered orally, topically or systemically to warm-blooded animals, e.g. humans, pigs or horses, in a vehicle comprising one or more pharmaceutically acceptable

20

carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For oral administration, the compound or a therapeutically acceptable salt thereof can be formulated in unit dosage

5   forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier. For topical administration, the compound can be formulated in pharmaceutically accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the active agent.

10   Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of formula 1 is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by

15   injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

20   Suitable vehicles or carriers for the above noted formulations are described in standard pharmaceutical texts, e.g. in "Remington's The Science and Practice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland,

25   1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small

30   increments until the optimum effect under the circumstance is reached. In general, the compound of formula 1 is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound or a therapeutically acceptable salt is administered in the range of 10 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 150 mg per kilogram.

5   With reference to topical application, the compound of formula 1 is administered topically in a suitable formulation to the infected area of the body e.g. the skin, the eye, the genitalia or part of the oral cavity, in an amount sufficient to cover the infected area. The treatment should be repeated, for example, every four to six hours until lesions heal.

10

For ocular administration, the compound of formula 1 is administered either topically or intraocularly (injection or implant) in a suitable preparation. For example, an implant containing the compound in a suitable formulation can be surgically placed in the posterior segment of the eye through a small

15   incision.

With reference to systemic administration, the compound of formula 1 is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. However, a

20   dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

Although the formulations disclosed hereinabove are indicated to be

25   effective and relatively safe medications for treating herpes viral infections, the possible concurrent administration of these formulations with other antiviral medications or agents to obtain beneficial results also included. Such other antiviral medications or agents include the antiviral nucleosides, for example, acyclovir, penciclovir, famciclovir, valacyclovir and ganciclovir,

30   and antiviral surface active agents or antiviral interferons such as those disclosed by S.S. Asculai and F. Rapp in U.S. patent 4,507,281, March 26, 1985.

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The following examples further illustrate and teach this invention.
Temperatures are given in degrees Celsius. Solution percentages or ratios
express a volume to volume relationship, unless stated otherwise. Nuclear
magnetic resonance spectra were recorded on a Bruker 400 MHz

5   spectrometer; the chemical shifts (δ) are reported in parts per million.
Abbreviations or symbols used in the examples include ATP: adenosine
triphosphate; Bu: butyl; i-Pr₂NEt: diisopropylethylamine; DMF: dimethyl-
formamide; DMSO: dimethylsulphoxide; Et: ethyl; EtOAc: ethyl acetate;
Et₂O: diethyl ether; Et₃N: triethylamine; ESI/MS: electro spray ionization

10   mass spectrometry; mAb: monoclonal antibody; Me: methyl; MeOH:
methanol; PFU: plaque forming units; Ph: phenyl; Pr: propyl; TBTU: 2-(1*H*-
benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate; THF:
tetrahydrofuran.

EXAMPLES

15

Example 1

N-Butyl-N-methyl-3-{(4-chloro-2-hydroxybenzoyl)amino}benzamide
(1:R₁=OH, R₂, R₄ and R₅=H, R₃=C1 and R=N(Me)Bu)
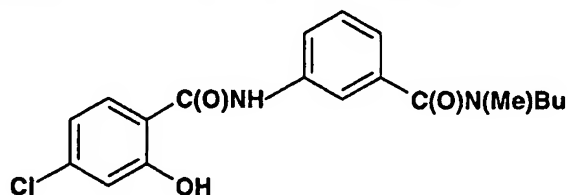
20

**(a) Ethyl 3-{(4-chloro-2-methoxybenzoyl)amino}benzoate (4: R₁ₐ = OMe,
R₂ and R₄ = H, R₃ₐ = Cl, R₅ = H and Rₐ = Et)**
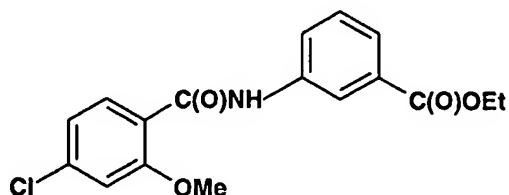
25   A suspension of 4-chloro-2-methoxybenzoic acid (10.0 g, 53.6 mmol), oxalyl
chloride (8.84 g, 69.7 mmol) and DMF (50 µL) in CH₂Cl₂ (107 mL) was

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stirred at 25° for 2 h. The resulting clear solution was concentrated under
reduced pressure. To the residual, crude acyl chloride in CH_2Cl_2 (107 mL)
were added ethyl 3-aminobenzoate (8.85 g, 53.6 mmol) and Et_3N (10.8 g,
107 mmol) over 5 min at 25°. The mixture was stirred at 25° for 24 h. The
resulting suspension was diluted with EtOAc (350 mL) and the resulting
solution was successively washed with aqueous 1 N HCl (2×150 mL),
aqueous saturated $NaHCO_3$ (2×150 mL) and brine (150 mL). The organic
layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure
to give the desired benzoylaminobenzoate of formula 4 (17.4 g, 97% yield)
as a beige solid: ^{1}H NMR (DMSO-d_6) δ 10.31 (s, 1H), 8.40 (broad s, 1H),
7.94 (broad d, J = 7.9 Hz, 1H), 7.69 (dt, J = 7.9, 1.2 Hz, 1H), 7.62 (d, J = 8.2
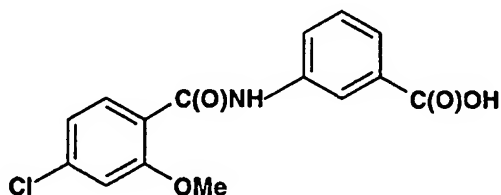Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.28 (d, J =1.9 Hz, 1H), 7.13 (dd, J = 8.2,
1.9 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H).

(b) 3-{(4-Chloro-2-methoxybenzoyl)amino}benzoic acid (5: R_{1A} = OMe,
R_2 and R_4 = H, R_{3A} = Cl and R_5 = H)

A solution of ethyl 3-{(4-chloro-2-methoxybenzoyl)amino}benzoate (12.2 g,
36.5 mmol), aqueous 1 N NaOH (55 mL, 55 mmol) in THF (75 mL) and
MeOH (50 mL) was stirred at 25° for 6 h. Water (50 mL) was added and
most of the THF/MeOH solvent was removed under reduced pressure.
Water (100 mL) and Et_2O (50 mL) were added and the phases were
separated. The aqueous layer was rendered acidic (pH < 2) by addition of
aqueous 1 N HCl and EtOAc (300 mL) was added. The insoluble benzoic
acid derivative of formula 5 was collected by filtration. The organic phase of
the filtrate was concentrated under reduced pressure. The residue was
dissolved in THF (40 mL) and poured into water (300 mL). The resulting
suspension was filtered to give an additional portion of the benzoic acid

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derivative (total of 10.4 g, 93% yield for 2 fractions): ^{1}H NMR (DMSO-d$_6$) δ
11.60 (broad s, 1H), 10.27 (s, 1H), 8.37 (broad s, 1H), 7.91 (broad d, J = 7.9
Hz, 1H), 7.67 (dt, J = 7.9, 1.3 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.46 (t, J =
7.9 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.13 (dd, J = 8.3, 1.9 Hz, 1H), 3.92 (s,
5   3H).

(c) *N*-Butyl-*N*-methyl-3-{(4-chloro-2-methoxybenzoyl)amino}benzamide
(7: R$_{1A}$=OMe, R$_2$, R$_4$ and R$_5$=H, R$_{3A}$=Cl and R$_B$=N(Me)Bu)
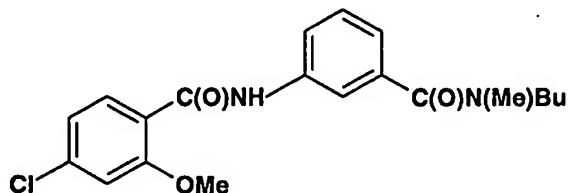
10   To a solution of 3-{(4-chloro-2-methoxybenzoyl)amino}benzoic acid (0.30 g,
0.98 mmol), *N*-butyl-*N*-methylamine (103 mg, 1.18 mmol) and *i*-Pr$_2$NEt (380
mg, 2.94 mmol) in DMF (2.0 mL) at 25° was added TBTU (315 mg, 0.98
mmol). The mixture was stirred at 25° for 1.5 h. The mixture was diluted
with EtOAc (80 mL). The resulting solution was washed with aqueous 1 N
15   HCl (2×30 mL), aqueous saturated NaHCO$_3$ (2×30 mL), water (30 mL) and
brine (30 mL), dried (MgSO$_4$), filtered and concentrated under reduced
pressure to give the desired benzoylaminobenzoyl derivative of formula 7
(354 mg, 96% yield) as a yellowish oil-foam: ^{1}H NMR (DMSO-d$_6$) δ.(1:1
mixture of rotamers) 10.20 (s, 1H), 7.77 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H),
20   7.63 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H),
7.13 (dd, J = 8.3, 1.9 Hz, 1H), 7.03-7.09 (m, 1H), 3.92 (s, 3H), 3.44, 3.19 (2
broad s, 2H), 2.94, 2.88 (2 broad s, 3H), 1.62-1.45 (m, 2H), 1.40-1.27, 1.17-
1.05 (2m, 2H), 0.99-0.88, 0.81-0.71 (2m, 3H).

25   **(d) *N*-Butyl-*N*-methyl-3-{(4-chloro-2-hydroxybenzoyl)amino}benzamide**
(the title compound of formula 1 of this example)

25

AlCl$_3$ (307 mg, 2.30 mmol) was added to a solution of *N*-butyl-*N*-methyl-3-
{(4-chloro-2-methoxybenzoyl)amino}benzamide (345 mg, 0.92 mmol) in
CH$_2$Cl$_2$ (3.7 mL) at 25°. The mixture was kept at 25° for 17 h. The mixture
then was partitioned between EtOAc (75 mL) and aqueous 1 N HCl (50 mL).
5   The organic layer was dried (MgSO$_4$), filtered and concentrated under
reduced pressure. The residue was purified by flash chromatography (10-
40 μ silica gel, EtOAc:hexane, 1:1) to give the title compound (272 mg, 82%
yield) as a white foam: ^{1}H NMR (DMSO-d$_6$) δ (1:1 mixture of rotamers) 11.97
(s, 1H), 10.43 (s, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.79-7.74 (m, 1H), 7.74-7.67
10   (m, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.14-7.09 (m, 1H), 7.05-7.03 (m, 2H), 3.50-
3.40, 3.26-3.15 (2m, 2H), 3.30 (s, 3H), 2.95, 2.89 (2s, 3H), 1.62-1.44 (m,
2H), 1.40-1.04 (m, 2H), 1.00-0.89, 0.81-0.69 (2m, 3H); MS (ESI) m/z
361/363 (MH)$^+$.

15   **Example 2**

**4-Chloro-2-hydroxy-N-{3-(1-oxohexyl)phenyl}benzamide (1: R$_1$=OH, R$_2$,
R$_4$ and R$_5$=H, R$_{3A}$=Cl and R=NH-(CH$_2$)$_4$Me)**
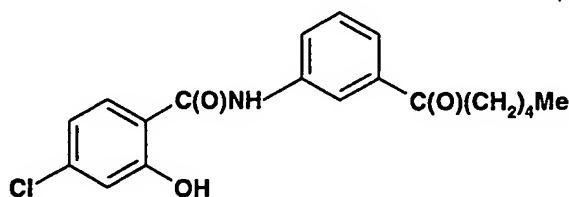
20

**(a) 3-{(4-Chloro-2-methoxybenzoyl)amino}-*N*-methoxy-*N*-
methylbenzamide (6: R$_{1A}$=OMe, R$_2$, R$_4$ and R$_5$=H, and R$_{3A}$=Cl)**

26
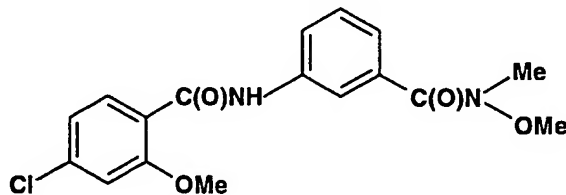
TBTU (4.73 g, 14.7 mmol) was added to a solution of 3-{(4-chloro-2-
methoxybenzoyl)amino}benzoic acid (4.50 g, 14.7 mmol), *N,O*-
dimethylhydroxylamine hydrochloride (1.72 g, 17.7 mmol) and *i*-Pr$_2$NEt (7.60
g, 58.9 mmol) in DMF (29 mL) at 25°. The reaction mixture was stirred at

5   25° for 2.5 h. The mixture was diluted with EtOAc (200 mL). The resulting
solution was successively washed with aqueous 1 N HCl (2x75 mL), water
(2x75 mL), aqueous saturated NaHCO$_3$ (2x75 mL) and brine (75 mL), then
dried (MgSO$_4$), filtered and concentrated under reduced pressure to give the
corresponding N-methoxy-N-methylbenzamide of formula 6 (4.32 g, 84%

10   yield) as a white solid: ^{1}H NMR (DMSO-d$_6$) δ 10.23 (s, 1H), 7.99 (broad s,
1H), 7.79 (broad d, J = 7.9 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.41 (t, J = 7.9
Hz, 1H), 7.29 (dt, J = 7.9, 1.3 Hz, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.13 (dd, J =
8.2 Hz, 1.9 Hz, 1H), 3.92 (s, 3H), 3.57 (s, 3H), 3.26 (s, 3H).

15   **(b) 4-Chloro-2-hydroxy-*N*-{2-(1-oxohexyl)phenyl}benzamide (the title
compound of formula 1 of this example)**

A 2.0 M solution of *n*-pentylmagnesium bromide in Et$_2$O (12.1 mL, 24.2
mmol) was added over 5 min to a solution of 3-{(4-chloro-2-

20   methoxybenzoyl)amino}-*N*-methoxy-*N*-methylbenzamide (1.69 g, 4.84 mmol)
in THF (48 mL) at 25°. The mixture was stirred at 25° for 1 h and aqueous 1
N HCl (15 mL) was added. The mixture was partitioned between EtOAc
(200 mL) and aqueous 1 N HCl (50 mL). The organic layer was
successively washed with water (50 mL) and brine (50 mL), then dried

25   (MgSO$_4$), filtered and concentrated under reduced pressure. The residue
was dissolved in CH$_2$Cl$_2$ (19 mL) and AlCl$_3$ (1.61 g, 12.1 mmol) was added
to the solution at 25°. After 2 h, a second portion of AlCl$_3$ (1.61 g, 12.1
mmol) was added to the mixture. The reaction mixture was stirred an
additional 2.5 h before aqueous 1 N HCl (25 mL) was added. The mixture

30   was partitioned between EtOAc (250 mL) and aqueous 1 N HCl (50 mL).
The organic layer was washed with brine (50 mL), dried (MgSO$_4$) and
concentrated under reduced pressure. The residue was purified by flash

chromatography (10-40 μ silica gel, hexane:EtOAc, 6:1) to afford the title

compound (1.05 g, 63% yield) as a beige solid: ^{1}H NMR (DMSO-d$_6$) δ 11.98

(s, 1H), 10.53 (s, 1H), 8.29 (broad s, 1H), 7.96 (broad d, J = 7.9 Hz, 1H),

7.94 (d, J = 8.9 Hz, 1H), 7.75 (broad d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.9 Hz,

5   1H), 7.05-7.03 (m, 2H), 3.00 (t, J = 7.1 Hz, 2H), 1.63 (quint., J = 7.1 Hz, 2H),

1.36-1.28 (m, 4H), 0.88 (t, J = 6.7 Hz, 3H); MS (ESI) m/z 368/370 (MNa)$^+$;

Anal. Calcd for $C_{19}H_{20}NO_3Cl$: C, 64.26; H, 5.07; N, 4.41. Found: C, 64.12;

H, 4.74; N, 4.33.

10   **Example 3**

Ethyl α-butyl-3-{(4-chloro-2-hydroxybenzoyl)amino}-β-

oxobenzenepropanoate (1: R$_1$=OH, R$_2$, R$_4$ and R$_5$=H, R$_3$=Cl and

R=CH(C(O)OEt)(CH$_2$)$_3$Me)
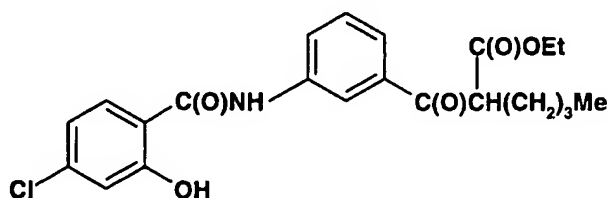
(a) Ethyl α-(2-butenyl)-3-nitro-β-oxobenzenepropanoate
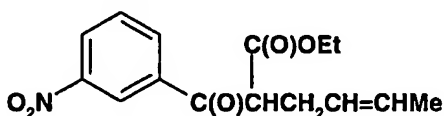
A 60% dispersion of NaH in mineral oil (917 mg, 22.9 mmol) was added over

20 min to a solution of ethyl 3-nitro-β-oxobenzenepropanoate (5.00 g, 21.1

20   mmol) in THF (50 mL) at such a rate to maintain a gentle reflux. The

mixture was stirred at 25° for 30 min and a solution of crotyl bromide (2.95

g, 21.9 mmol) in THF (15 mL) was added over 50 min. The reaction mixture

was stirred at 25° for 45 min and then heated at reflux for 16 h. Hexane

(100 mL) was added to the cooled mixture. The resulting suspension was

25   filtered and the filtrate was concentrated under reduced pressure. The

residue was dissolved in EtOAc and the resulting solution was washed with

28

aqueous 10% citric acid (2x), aqueous saturated NaHCO$_3$ (2x) and brine

then was dried (MgSO$_4$) and concentrated under reduced pressure. The

residue was purified by flash chromatography (40-63 μ silica gel,

hexane:EtOAc, 9:1) to afford ethyl α-(2-butenyl)-3-nitro-β-

5   oxobenzenepropanoate (4.60 g, 75% yield): ^{1}H NMR (CDCl$_3$) δ 8.83 (dd, J =

2.2, 1.2 Hz, 1H), 8.46 (ddd, J = 7.9, 2.2, 1.2 Hz, 1H), 8.31 (dt, J = 7.9, 1.2

Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 5.61-5.52 (m, 1H), 5.39-5.37 (m, 1H), 4.35

(t, J = 7.2 Hz, 1H), 4.17, 4.14 (2q, J = 7.0, 7.0 Hz, 2H), 2.77 (broad t, J = 7.2

Hz, 2H), 1.62 (dd, J = 6.4, 1.3 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H).

10

(b) Ethyl 3-amino-α-butyl-β-oxobenzenepropanoate.
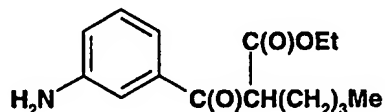
A solution of ethyl α-(2-butenyl)-3-nitro-β-oxobenzenepropanoate (411 mg,

1.41 mmol) in 1,4-dioxane (12 mL) was stirred at 25° for 8.5 h under a

15   hydrogen atmosphere (1 atm) in presence of Pd/BaSO$_4$ (225 mg + 150 mg

added after 5.5 h). The suspension was filtered (50 μ filter) and the filtrate

was concentrated under reduced pressure. The residue was purified by

flash chromatography (40-63 μ silica gel, hexane:EtOAc, 3:1) to give ethyl 3-

amino-α-butyl-β-oxobenzenepropionate (242 mg, 65% yield): ^{1}H NMR

20   (CDCl$_3$) δ 7.31 (broad d, J = 7.3 Hz, 1H), 7.27-7.23 (m, 3H), 6.88 (broad d, J

= 7.3 Hz, 1H), 4.22 (t, J = 7.2 Hz, 1H), 4.15, 4.14 (2q, J = 6.7, 6.7 Hz, 2H),

3.81 (broad s, 2H), 2.02-1.94 (m, 2H), 1.41-1.30 (m, 4H), 1.18 (t, J = 7.0 Hz,

3H), 0.89 (t, J = 6.7 Hz, 3H).

25   **(c) Ethyl α-butyl-3-{(4-chloro-2-hydroxybenzoyl)amino}-β-**

oxobenzenepropanoate (the title compound of formula 1 of this

example)

29

A solution of 4-chlorosalicylic acid (109 mg, 0.63 mmol) and oxalyl chloride
(175 mg, 1.38 mmol) and DMF (50 μL) in CH_2Cl_2 (5.0 mL) was stirred at 25°
for 1 h. The mixture was concentrated under reduced pressure. The
residue was dissolved in CH_2Cl_2 (3.0 mL). A solution of ethyl 3-amino-α-

5   butyl-β-oxobenzenepropanoate (133 mg, 0.51 mmol) in CH_2Cl_2 (5.0 mL) was
added followed by Et_3N (152 mg, 1.51 mmol). The reaction mixture was
stirred at 25° for 20 h. The mixture was concentrated under reduced
pressure and the residue was dissolved in EtOAc. The resulting solution
was washed with aqueous saturated $NaHCO_3$ (2x) and brine, then dried

10   $(MgSO_4)$, filtered and concentrated under reduced pressure. The residue
was purified by flash chromatography (40-63 μ silica gel, hexane:EtOAc,
4:1) to give the title compound of this example (100 mg, 48% yield) as a
white solid: mp 83-88°; ^1H NMR $(CDCl_3)$ δ; 12.00 (broad s, 1H), 8.50 (s, 1H),
8.11 (t, J = 1.4 Hz, 1H), 7.96 (dd, J = 7.9, 1.4 Hz, 1H), 7.77 (dd, J = 8.6 Hz,

15   1H), 7.48 (t, J = 7.9 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.87 (dd, J = 8.6, 2.0
Hz, 1H), 4.28 (t, J = 7.1 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 2.02-1.94 (m, 2H),
1.36-1.28 (m, 4H), 1.18 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H); MS (ESI)
418/420 $(MH)^+$.

20   **Example 4**

4-Chloro-2-hydroxy-N-{3-(1-oxohexyl)phenyl}benzamide.
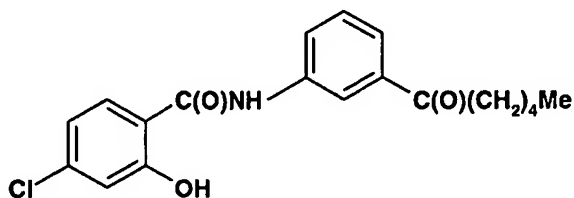
A solution of ethyl α-butyl-3-[(4-chloro-2-hydroxybenzoyl)amino]-β-

25   oxobenzenepropanoate (32.0 mg, 77.0 μmol) and $LiOH·H_2O$ (11.0 mg, 0.26
mmol) in THF (3.0 mL) and water (1.5 mL) was heated to 55° for 48 h. The
mixture was partitioned between water and EtOAc. The aqueous layer was
acidified with aqueous 10% citric acid then extracted with EtOAc. The

30

combined organic layers were dried (MgSO$_4$), filtered and concentrated
under reduced pressure. The residue was purified by reversed phase HPLC
(Whatman Partisil® ODS-3 C$_{18}$ 10 µ, 22 x 500 mm; 0 to 80% MeCN +
0.06% TFA / water + 0.06% TFA) to give the title compound (16.0 mg, 60%
5   yield) as a white solid: mp 134-136°; identical to the product of example 2.

Example 5

The following two assays (i and ii) were used to evaluate antiherpes activity.
10
i) HSV-1 helicase-primase DNA primase assay

The HSV-1 helicase-primase enzyme used for primase assays was expressed and
isolated as described (M.S. Dodson et al., *J. Biol. Chem.* **1989**, *264*, 20835; S.
15   Dracheva et al. *J. Biol. Chem.* **1995**, *270*, 14148) except that the UL5-expressing
baculovirus was changed to express UL5(K103A). The resulting altered enzyme
contained no detectable helicase, DNA-dependent ATPase, or ATPase activity.
However, DNA primase activity was increased over the wild type enzyme.

20   Assay: DNA primase activity was measured by the incorporation of [³H]GTP into
newly synthesized primers by the UL5(K103A) helicase-primase holoenzyme.
Assays were performed using as template the 50-mer single-stranded DNA
oligonucleotide 5'-CTTCTTCGGT TCCGACTAC CCCTCCCGAC TGCCTATGAT
GTTTATCCTT T G-3'OH (SEQ ID No. 1) derived from the preferred priming site on
25   φX174 single-stranded DNA [D.J. Teney et al., *J. Biol. Chem.* **1995**, *270*, 9129-
9136]. The reaction mixtures (60 µl) contained 20 mM Tris-HCl pH 8.0, 5 mM
magnesium chloride, 1 mM DTT, 0.01% CHAPS, 100 µM each of ATP, GTP, CTP,
10 µM [biotin]UTP, 1 µCi [³H]GTP (specific activity 30.8 Ci/mmol),1 µg of the 50-
mer template and 45 µg/ml of the UL5(K103A)-altered helicase-primase
30   holoenzyme. The samples were incubated at 34° for 45 min in a circulating
waterbath and reactions were quenched by the addition of 20 µl 0.5 M EDTA pH 8.
Then, 50 µl of the reaction mixtures were transferred to Millipore filtration plates

31

(MHVB N45, 0.45 μm) containing 40 μl of immobilized avidin beads (Pierce). After
incubating 30 min at room temperature on a microplate shaker, the wells were
washed five times with 300 μl wash buffer (50 mM 4-(2-hydroxyethyl)-1-
piperazineethanesulfonic acid (HEPES) pH 7.5 and 0.5 M NaCl) and the filter plates

5   were aspirated to dryness. The radioactivity in each well was counted using the
Topcount® after adding 100 μl Microscint® 20 (Camberra-Packard Canada,
Mississauga, Ontario, Canada) to each well.

IC$_{50}$ DETERMINATIONS

10   In all cases, compounds were tested in three-fold serial dilutions and the
results were expressed as percent inhibition as compared to control
reactions without inhibitor. IC_{50} (i.e., inhibitor concentration that yielded 50%
inhibition of enzyme activity) values were determined from dose-response
curves using SAS software (SAS Institute, Cary, North Carolina, USA). A

15   non-linear regression analysis based on the Hill equation, M. Dixon and E.C.
Webb *Enzymes*, Academic Press: New York, NY, USA, 1979, was applied
to the percent inhibition-concentration data.

ii) Inhibition of Herpes Simplex Virus (HSV-1) Replication in Cell Culture

20

Assay: BHK-21 cells clone 13 (ATCC CCL10) were incubated for two days in
850 cm^2 roller bottles (2x10^7 cells/bottle) with α-MEM medium (Gibco
Canada Inc., Burlington, Ontario, Canada) supplemented with 8% (v/v) fetal
bovine serum (FBS, Gibco Canada, Inc.). The cells were trypsinized and

25   then 3,000 cells in 100 μL of fresh medium were transferred into each well of
a 96-well microtiter plate. The cells were incubated at 37° for a period of 3
days to reach a density of 50,000 cells per well.   The cells were washed
twice with 100 μL of α-MEM supplemented with 2% heat inactivated FBS
and incubated for 1-2 h in 100 μL of the same medium.

30

Thereafter, the cells were infected with HSV-1 strain F or KOS (multiplicity of
infection = 0.05 PFU/cell) in 50 μL of α-MEM supplemented with 2% heat

32

inactivated FBS. Following one hour of virus absorption at 37°, the medium
was removed and the cells were washed with α-MEM supplemented with 2%
heat inactivated FBS (2 x 100 μL). The cells were incubated with or without
100 μL of the appropriate concentration of test reagent in α-MEM medium

5   supplemented with 2% heat inactivated FBS.   After 24 h of incubation at
37°, the extent of viral replication was determined by an ELISA assay; for
instance, the following assay that detects the late glycoprotein C of HSV-1.

Cells were fixed in the microtiter plate with 100 μL of 0.063% glutaraldehyde

10   in phosphate buffered saline for 30 min at room temperature. The microtiter
plate was then washed once with casein blocking solution and blocked with
200 μL of the same solution for 1 h at room temperature. Thereafter, 100 μ
L of mAb C11 recognizing the glycoprotein C of HSV-1 (see E. Trybala et
al., Journal of General Virology, **1994**, *75*, 743) was added to each well for 2

15   h at room temperature. The plate was washed three times with phosphate
buffered saline containing 0.05% polyoxyethylene (20) sorbitan monooleate.
The cells were incubated with 100 μL of sheep anti-mouse IgG horseradish
peroxidase for 1 h at room temperature in the dark.
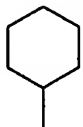
20   The plate was washed three times with 200 μL of the above-noted
phosphate buffer saline preparation, and then once with 0.1 M sodium
citrate (pH 4.5). Thereafter, 100 μL of orthophenylenediamine
dihydrochloride (OPD, Gibco, Canada Inc.) was added to each well. The
plate was agitated on a microplate shaker for 30 min in the dark. Color

25   development was monitored at 450 nm using a microplate
spectrophotometer.

SAS was used to calculate % inhibition of viral replication and to generate
EC_{50} values.

30
The results from assays i and ii for compounds are noted in TABLE 3.
Results for assay i are expressed under the heading HSV-1, IC_{50} (μM).
Results for assay ii are expressed under the heading HSV-1, EC_{50} (μM). In
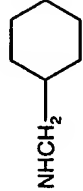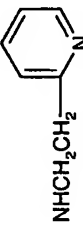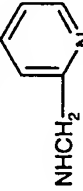
both instances category "A" includes compounds having an IC_{50} or an EC_{50} of less than about 1 μM; category "B" includes compounds having an IC_{50} or an EC_{50} falling within the range of about 1-100 μM; and category "C" includes compounds having an IC_{50} or an EC_{50} of greater than about 100μM.
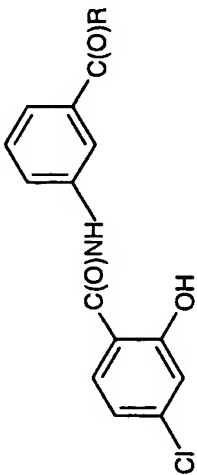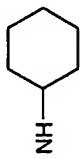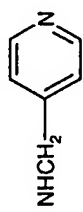
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TABLE 1

Compound of formula 1 having the structure

BILS #	Entry No.	R	ESI/MS (m/z) (M+H)+, unless noted otherwise, and isotopic peak due to chlorine	HPLC[1] Purity (%)
867	1	CH(C(O)OEt)(CH$_2$)$_3$Me	418/410	93.3
868	2	Me	290/292	97.4
872	3	CH$_2$C(O)OEt	362/364	87 (7% enol)
883	4	(CH$_2$)$_2$Me	340/342*	99.5
884	5	CH$_2$Ph	364/366**	98.4
885	6		356/358**	99.9
893	7	CH$_2$CH$_2$Ph	378/380**	97.3
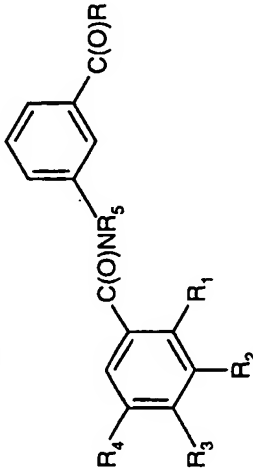
Compound of formula 1 having the structure

BILS #	Entry No.	R	ESI/MS (m/z) (M+H)[+], unless noted otherwise, and isotopic peak due to chlorine	HPLC[1] Purity (%)
886	8	OCH₂-pyridine	381/383**	98.2
901	9	OCH₂Ph	380/382**	99
878	10	piperidine	381/383*	99.7
879	11	N(Me)CH₂CH₂-pyridine	410/412	99.7
880	12	N(Me)(CH₂)₃Me	361/363	99.6

36

Compound of formula 1 having the structure

BILS #	Entry No.	R	ESI/MS (m/z) (M+H)+, unless noted otherwise, and isotopic peak due to chlorine	HPLC[1] Purity (%)
888	13	NHCH2–cyclohexyl	409/411*	100
889	14	NHCH2CH2–pyridine	396/398	98.1
890	15	NHCH2Ph	403/405*	93.7
877	16	NH(CH2)3Me	369/371*	99.4
881	17	NHCH2–pyridine	382/384	100

Compound of formula 1 having the structure

BILS #	Entry No.	R	ESI/MS (m/z) (M+H)+, unless noted otherwise, and isotopic peak due to chlorine	HPLC[1] Purity (%)
882	18	cyclohexyl-NH	395/397*	97.1
892	19	pyridyl-NHCH2	380/382**	99.8

[1] HPLC conditions: Vydac®,C$_{18}$,5µ, 15cm; solvent: 5-100% MeCN + 0.06% TFA/H$_2$O+0.06% TFA in 25 min; UV detector: 230 nm

* (M + Na)+

** (M – H)-

TABLE 2

Compound of formula 1 having the structure

BILS #	Entry No.	R₁	R₂	R₃	R₄	R₅	R	ESI/MS (m/z) (M+H)⁺, unless noted otherwise, and if present isotopic peak due to chlorine	HPLC[1] Purity (%)
876	101	OH	Cl	H	H	H	(CH₂)₄Me	344/346**	97.2
895	102	OH	H	Me	H	H	NHCH₂Ph	359/361**	97.5
896	103	OH	H	OMe	H	H	NHCH₂Ph	375/377**	96.8
897	104	OH	H	N₃	H	H	NHCH₂Ph	386**	99.2
898	105	NH₂	H	H	H	H	NHCH₂Ph	346	95.8
899	106	OH	H	N₃	—	H	NHCH₂Ph	514	100
902	107	NH₂	H	Cl	H	H	NHCH₂Ph	380/382	95.8
903	108	OH	H	NH₂	H	H	NHCH₂Ph	362/364	95.0
MEN 2161	109	OH	H	Cl	H	H	NHCH₂Ph	368/370*	98.7
MEN	110	OH	H	H	Cl	H	NHCH₂Ph	346/348	100.0

Compound of formula 1 having the structure

BILS #	Entry No.	R_1	R_2	R_3	R_4	R_5	R	ESI/MS (m/z) $(M+H)^+$, unless noted otherwise, and if present isotopic peak due to chlorine	HPLC[1] Purity (%)
MEN 2163	111	OH	H	H	H	H	$NHCH_2Ph$	311	99.0
MEN 1941	112	OH	H	OH	H	H	$NHCH_2Ph$	328	100.0
MEN 2141 887	113	OH	H	H	H	Me	$NHCH_2Ph$	358/360**	98.2

1   HPLC conditions: Vydac®, C_{18} 5μ 15cm; solvent: 5-100% MeCN + 0.06% TFA/H_2O + 0.06% TFA in 25 min; UV detector: 230 nm
* $(M + Na)^+$
** $(M - H)^-$

5

TABLE 3

Enzyme inhibition and cell culture data of compounds in Tables 1 and 2		
Compound Entry No.	HSV-1 IC_{50} (μM)	HSV-1 EC_{50} (μM)
1	B	B
2	B	B
3	B	B
4	B	B
5	B	B
6	B	B
7	B	-
8	A	B
9	A	-
10	C	>A
11	C	
12	C	>A
13	A	B
14	B	B
15	A	B
16	B	B
17	A	B
18	B	>A
19	B	-
101	B	B
102	A	-
103	A	-
104	A	-
105	C	-
106	A	-
107	C	-
108	B	-
109	B	-
110	B	B
111	B	B
112	C	-
113	C	-
114	B	-

What is claimed is:

1. A compound of formula 1

(1)

wherein

R_1 is hydroxy or amino;

R_2 is hydrogen, halo, (C_{1-4})alkyl or (C_{1-4})alkoxy;

R_3 is hydrogen, halo, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino or azido;

R_4 has the same significance as R_2;

R_5 is hydrogen or (C_{1-4})alkyl; and

R is (C_{1-7})alkyl, (C_{3-8})cycloalkyl,

{phenyl(C_{1-7})alkyl}, {phenyl(C_{1-7})alkoxy}, {{(monocyclic heterocyclo)-{(C_{1-7})alkoxy}}, CH(W)C(O){O-(C_{1-4})alkyl} wherein W is hydrogen or (C_{1-7})alkyl, or

$$N \overset{Y}{\underset{Z}{\diagdown}}$$

wherein Y in hydrogen or (C_{1-7})alkyl, and Z is (C_{1-7})alkyl, (C_{3-6})cycloalkyl, {(C_{3-6})cycloalkyl}-

{(C_{1-7})alkyl}, phenyl(C_{1-7})alkyl or {{(monocyclic heterocyclo)-{(C_{1-7})alkyl}}, or

Y and Z together with the nitrogen atom to which they are attached

represent, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or 1-(4-

methylpiperazinyl);

with the provisos that (1) when R is CH(W)C(O)-

{O-(C_{1-4})alkyl} as defined herein, then R_5 is hydrogen; and (2) at least one of

R_2, R_3 and R_4 is other than hydrogen;

or a salt thereof.

2. A compound according to claim 1, wherein R_1 is hydroxy.

3.   A compound according to claim 1, wherein R_2 is hydrogen or halo.

4.   A compound according to claim 1, wherein R_2 is hydrogen or chloro.

5

5.   A compound according to claim 1, wherein R_2 is hydrogen.

6.   A compound according to claim 1, wherein R_3 is hydrogen, chloro, methyl, methoxy, amino or azido.

10

7.   A compound according to claim 1, wherein R_3 is methyl, methoxy, amino or azido.

8.   A compound according to claim 1, wherein R_4 is hydrogen or halo.

15

9.   A compound according to claim 1, wherein R_4 is hydrogen, chloro or iodo.

10.   A compound according to claim 1, wherein R_5 is hydrogen or methyl.

20

11.   A compound according to claim 1, wherein R_5 is hydrogen.

12.   A compound according to claim 1, wherein R is methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, cyclohexyl, phenylmethyl, 2-phenylethyl,

25   phenylmethoxy, 2-phenylethoxy, 2-, 3- or 4-pyridinylmethoxy, 2-(2-,3- or 4-pyridinyl)ethoxy, $CH_2C(O)\{O-\{(C_{1-4})alkyl\}\}$, $CH\{(C_{1-7})alkyl\}C(O)\{OC_{1-4})alkyl\}$, (C_{1-7})alkylamino, cyclopentylamino, cyclohexylamino, (cyclohexylmethyl)amino, (2-cyclohexylethyl)amino, (phenylmethyl)amino, (2-phenylethyl)amino, 2-(3- or (4-pyridylmethyl)amino

30   or 2-(2-, (3- or (4-pyridylethyl)amino.

43

13.   A compound according to claim 1 wherein R is pentyl, hexyl, cyclohexyl, phenylmethyl, 2-phenylethyl, phenylmethoxy, 2-, 3- or 4-pyridinylmethoxy, $CH_2C(O)OCH_2CH_3$, $CH(CH_2CH_2CH_2CH_3)C(O)OCH_2CH_3$, ethylamino, propylamino, butylamino, cyclohexylamino, (cyclohexylmethyl)-amino, (2-cyclohexylethyl)amino, (phenylmethyl)amino, (2-phenylethyl)amino, or (2-, (3- or (4-pyridylmethyl)amino, or 2-(2-, (3-, or (4-pyridinylethyl)amino.

14.   A pharmaceutical composition for the treatment or prevention of a disease or condition involving herpes virus, comprising an effective amount of a compound according to claim 1, and a pharmaceutically acceptable carrier or auxiliary agent.

15.   Use of a compound according to claim 1, for the manufacture of a medicament for treating a herpes virus infection in a mammal.

16.   The use of claim 15, wherein said medicament is administered to said mammal in conjunction with an additional antiviral agent.

17.   The use of claim 16, wherein the additional antiviral agent is selected from acyclovir, pencyclovir, famciclovir, valaciclovir and ganciclovir.

18.   A method for inhibiting herpes virus replication, comprising exposing cells infected with herpes virus to a compound according to claim 1.

19.   A compound selected from:

,

, and

, or a salt thereof.
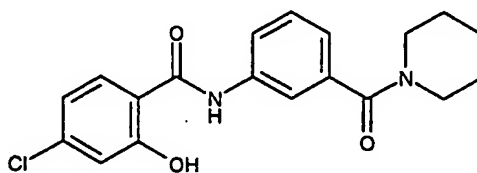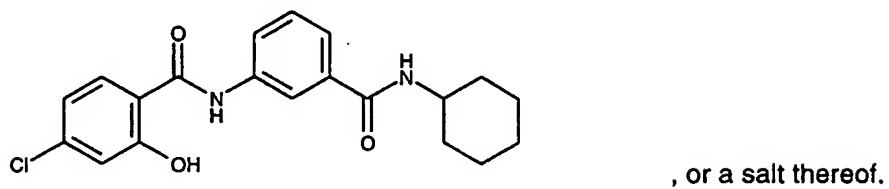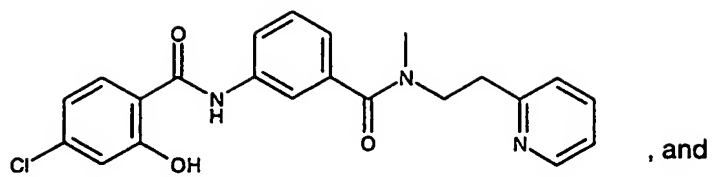
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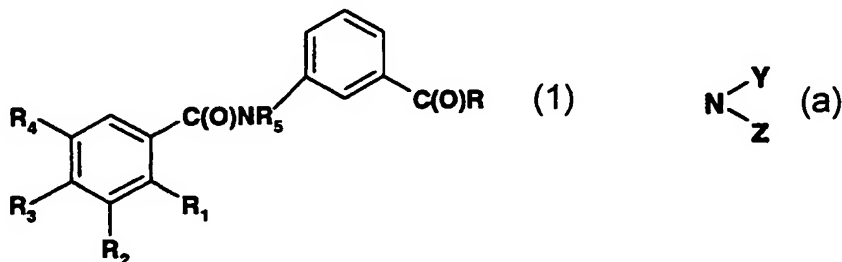
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HSV PRIMASE INHIBITORS

(57) Abstract: The invention provides compounds of formula (1) that are active against the HSV primase enzyme: wherein R_1 is hydroxy or amino; R_2 is hydrogen, halo, (C_{1-4})alkyl or (C_{1-4})alkoxy; R_3 is hydrogen, halo, (C_{1-4})alkyl, (C_{1-4})alkoxy, amino or azido; R_4 has the same significance as R_2; R_5 is hydrogen or (C_{1-4})alkyl; and R is (C_{1-7})alkyl, (C_{3-6})cycloalkyl, {phenyl(C_{1-7})alkyl}, {phenyl(C_{1-7})alkoxy}, {{(monocyclic heterocyclo)-{(C_{1-7})alkoxy}}, $CH(W)C(O)\{O-(C_{1-4})$alkyl} wherein W is hydrogen or (C_{1-7})alkyl, or (a) wherein Y is hydrogen or (C_{1-7})alkyl, and Z is (C_{1-7})alkyl, (C_{3-6}) cycloalkyl, {(C_{3-6})cycloalkyl}-{(C_{1-7})alkyl}, phenyl(C_{1-7})alkyl or {{(monocyclic heterocyclo)-{(C_{1-7})alkyl}}, or Y and Z together with the nitrogen atom to which they are attached represent, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl or 1-(4-methylpiperazinyl); with the provisos that (1) when R is $CH(W)C(O)-\{O-(C_{1-4})$alkyl} as defined herein, then R_5 is hydrogen; and (2) at least one of R_2, R_3 and R_4 is other than hydrogen.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   C07C237/42   A61P31/22   A61K31/165   C07D213/40   C07D295/18
C07C235/60   C07C235/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7   C07C   C07D   A61K   A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 497 816 A (UNIROYAL CHEMICAL LTD ;UNIROYAL CHEM CO INC (US)) 12 August 1992 (1992-08-12) cited in the application page 24 -page 26; claims ---	1,14,15, 18,19
A	US 5 258 407 A (WASHBURN WILLIAM N ET AL) 2 November 1993 (1993-11-02) column 7; example 16; table 1 --- -/--	1,14,15, 18,19

[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 December 2000	28/12/2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KONDRAT'EV, V. P. ET AL: "Effectiveness of novel salicylanilide derivatives for the treatment of fascioliasis in livestock" retrieved from STN Database accession no. 104:101982 CA XP002155157 abstract & DOKL. VSES. AKAD. S-KH. NAUK IM. V. I. LENINA (1985), (9), 32-4 , 1985, —————	1,14,15, 18,19

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